

ORIGINAL ARTICLES

Scientific and General

HYDATIDIFORM MOLE AND
CHORIONEPITHELIOMA*

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HYDATIDIFORM mole and chorionepithelioma are relatively rare conditions. Because they are so rare, and show such remarkable variations in clinical course, they are often poorly understood and therefore badly treated.

There have been, however, many advances in our knowledge of these two conditions in recent years and the present study is an attempt to summarize this knowledge. It is based upon the clinical and pathological findings in our own cases at the University of California Hospital, and upon a review of the recent literature.

SOURCE MATERIAL

We have observed sixteen cases of hydatidiform mole and eight chorionepitheliomas. Two cases appear in both groups; in one, a choriocarcinoma was present in the uterine wall, while the mole was still in the uterus; in the other, a syncytioma followed a mole under our observation. In two other cases of chorionepithelioma we were able to obtain slides of the preceding mole for study.

The pathological picture has been carefully reviewed in all cases. The moles were classified as benign or potentially malignant, according to the criteria of Hertig, while the chorionepitheliomas were divided into choriocarcinoma, choriadenoma and syncytioma, according to Ewing. Hormonal studies have been made on all cases since 1930; six of the moles and four of the chorionepitheliomas.

CLINICAL PICTURE

The clinical picture in the sixteen cases of hydatidiform mole was much as has been described in the literature. The ages of the patients with mole varied from twenty to forty-two years; only one patient was over forty and only four over thirty. The most frequent presenting symptom was irregular bleeding in association with a supposed pregnancy, while only two had no history of bleeding. All but two showed at least moderate anemia, and half of the patients showed leucocytosis of varying degree, the highest being 18,000. Sedimentation time varied from 35 minutes to 1½ hours for 18 m.m. in 9 cases.

Five of the sixteen cases had moderate nausea and vomiting, while four had hyperemesis. Two showed a preëclamptic toxemia.

Seven cases gave the classical picture of a uterus much larger than the supposed duration

of the pregnancy, and in three of these the rapid enlargement, while the patient was under observation, gave the clue to the diagnosis. Three cases had aborted the mole a few days previous to admission; in two cases the size of the uterus corresponded to the estimated duration of pregnancy; in one the duration of pregnancy was unknown; while in three the uterus was actually smaller than it should have been.

Lutein cysts were recognized in six of the women, in four from one to two months post partum.

Vesicles were not observed in any case before actual evacuation of the mole, although looked for many times.

The x-ray was used as an aid in diagnosis in four cases in which the uterus was larger than it should have been for the estimated age of the pregnancy. No evidence of a fetus was found in any of these. Chest x-rays were taken in three cases of patients who entered shortly after passing the mole. None showed evidence of pulmonary metastases.

TREATMENT

Thirteen patients were treated by simple evacuation of the uterus, after spontaneous, instrumental or bag dilatation of the cervix, or after vaginal hysterotomy. Two cases had immediate hysterectomies, one because of a fibromyoma, another because of a complicating choriocarcinoma. Still another had a hysterectomy a few days after instrumental evacuation of the mole, because the pathologic picture of the mole so strongly suggested malignant tendencies. The removed uterus showed no evidence of chorionepithelioma, and the Aschheim-Zondek test taken just preoperatively was negative. This was in the early days of the Aschheim-Zondek test before it was realized how much reliance could be placed upon it.

Two patients received radium, one a dose of 639 mch for bleeding one month following her mole. This woman later had two pregnancies, one full-term, one early therapeutic abortion. One woman received 1516 mch because of complicating fibroids, with permanent amenorrhea resulting.

COMMENT

Three patients were readmitted to the hospital for study because of symptoms suggesting the development of a chorionepithelioma. One of these had a chorionepithelioma of the syncytial endometritis type of Ewing; in the other two, chorionepithelioma was ruled out by curettage, substantiated in one case by negative hormonal studies.

None of the sixteen patients died as a result of the mole or its sequelae. One thirty-seven year old woman died, two years after her mole, of carcinoma of the hepatic duct. All the rest are known to be well at the present time except three, and these had been well for seven, ten, and fifteen years respectively, following their

* Read before the Section on Obstetrics and Gynecology, at the Seventy-first Annual Session of the California Medical Association, Del Monte, May 7, 1941.

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mole when last seen.

Since four of the women had hysterectomies at the time of their mole or shortly thereafter, and one had a sterilizing dose of radium, the possibility of further pregnancies remained in only eleven. One of these died two years after her mole of carcinoma of the hepatic duct; of the remaining ten, nine had from one to four further pregnancies and none had a second mole.

Of the eight chorionepitheliomas, three were choriocarcinomas, two choriadenomas, one a syncytioma, and one a case with pulmonary metastases in which the type of the primary lesion could not be classified with certainty.

Only one died—a patient with choriocarcinoma, who entered the hospital in practically moribund condition with vaginal and generalized abdominal metastases. The blue vaginal nodule was noticed by her physician at the time of curettage two months earlier, but its serious significance was apparently not realized until it began to take on very rapid growth and to slough six weeks later. In contrast to this patient was another who was referred for treatment immediately upon detection of a vaginal metastasis, while her physician was curetting her for a mole. With prompt radical operation this woman remained alive and well eight years later.

The great variability in behavior of both moles and chorionepitheliomas has led to numerous attempts on the part of pathologists to correlate the microscopical with the clinical picture. Opinion on this subject is very much divided. A very careful review of our material leads us to the conclusion that, although pathologic examination of the mole for the criteria of potential malignancy is often suggestive, it cannot be depended upon for practical purposes.

The pathological picture in three of the four cases of chorionepithelioma in which slides of the original mole were available fulfilled some of the criteria of potential malignancy as outlined by Hertic, but in one case the mole appeared of distinctly benign type. Furthermore, in four of the cases without malignant sequelae, the histologic picture was far more suggestive of potential malignancy than in any of the four with them. In one case this pathologic picture led to removal of the uterus which showed no evidence of chorionepithelioma.

We feel, therefore, that no matter how benign the microscopic picture, every mole must have a careful follow-up to detect at the earliest moment the possible development of a chorionepithelioma; yet, on the other hand, no mole should be considered actually malignant without corroborative evidence, and this will be furnished by the biologic pregnancy tests.

The proper interpretation of these tests is, however, not always simple. When it was first discovered by Zondek and by Meyer that hydatidiform mole and chorionepithelioma gave un-

usually high values of gonadotropic hormone in the urine it was felt by many that diagnosis had become a simple matter of quantitative estimation of this hormone, in spite of Aschheim's warning to the contrary. The interruption of a number of cases of normal twin pregnancy, and one triplet pregnancy where too rapid enlargement of the uterus plus high hormonal values had led to a diagnosis of mole, showed that the matter was not so simple as this. In 1937, Evans, Kohls and Wonder reported the normal occurrence of transient extremely high levels of gonadotropic hormone in the blood and urine of early pregnancy, and this work was confirmed by Palmer and others. A peak value is reached some time between the twentieth and the fiftieth day after the first missed period, which may equal or exceed any value as yet reported in hydatidiform mole or chorionepithelioma. However, following the peak, there is a very abrupt drop in hormone concentration, so that in all but one case values remained below 10,000 rat units per liter after the 65th day of pregnancy. For this reason Palmer feels that unusually high hormonal values in a pregnancy definitely past the first trimester would, in all probability, be diagnostic of mole.

The fact that the Aschheim-Zondek reaction may remain positive for many months after the passage of a mole, although it disappears within a week after the termination of a normal pregnancy, has long been recognized. Two explanations have been offered for this phenomenon: that of Phillip and Sigmund, who believe that the prolonged excretion is due to slow release of stored hormone from the accompanying lutein cysts, and that of Brindeau, Hinglais and Hinglais who feel that chorionic epithelium may persist for a considerable time in the uterine wall without undergoing malignant change, and may continue as a source of hormone. According to present opinion repeated quantitative estimations of chorionic gonadotropic hormone are our only means for the early detection of chorionepithelioma following mole. A single positive test, even many months later, is of no value whatsoever. So long as the titre is decreasing, or at least remains constant, we may safely observe the patient. If malignant change does occur, there is a sudden abrupt rise in hormone titre, sometimes after it has remained at a low point for a considerable length of time. With sufficiently frequent observation, this malignant change may be detected in ample time for radical treatment, and in one of the cases of Brindeau, Hinglais and Hinglais it occurred while the chorionepithelioma was still the size of a pea. Whether or not there may be a reappearance of hormone and malignant change after the hormone has once entirely disappeared is still a controversial point. Brindeau, Hinglais and Hinglais found no recurrence after complete disappearance, although they did find it after the hormone had reached very low levels, and with this most authorities agree. In one of our cases

the hormone reached such a low point that it required concentration methods to demonstrate it before the abrupt rise signaled the onset of the chorionepithelioma.

That the sudden abrupt rise in hormone titre may be due to the development of a new pregnancy rather than a chorionepithelioma must never be forgotten. Otherwise there is danger of interrupting a normal pregnancy or even of extirpating the pregnant uterus of a healthy young woman. Ordinarily clinical methods will establish this diagnosis readily enough if the possibility is kept in mind.

Until recently a positive reaction for chorionic gonadotropic hormone in the spinal fluid has been accepted by many as diagnostic of hydatidiform mole or chorionepithelioma, although very few studies had been made in normal pregnancy, and Hashimoto had reported positive Aschheim-Zondek reactions in five cases of normal pregnancy using from 18-20 c.c. of cerebrospinal fluid. Recent studies by Palmer, in the University of California Gynecologic Endocrine laboratory, showed six positive reactions for chorionic gonadotropic hormone in the cerebrospinal fluid among forty-two normally pregnant women, and one negative spinal fluid reaction in a woman with chorioadenoma.

It is therefore apparent that no one hormonal test suffices to establish absolutely the diagnosis of either hydatidiform mole or chorionepithelioma, no matter how high the value or whether it be made on blood, urine, or spinal fluid. Repeated quantitative determinations are of the utmost value in the follow-up of hydatidiform mole, and a sudden increase in titre after it has dropped to a low level is most suggestive of the development of a chorionepithelioma, providing always that the onset of a new pregnancy can be ruled out.

Complete disappearance of the hormone within a month after evacuation of a mole is the rule. However, long persistence of a positive reaction after a mole is in itself of no serious significance providing the titre is decreasing or at least remaining stationary, but an increase in titre must be most carefully evaluated at once. Weekly quantitative determinations and clinical examination are essential at first, and will allow the detection of malignant change in adequate time for successful treatment. After the test has once become entirely negative, even in a concentrated specimen, it will probably remain so, but further data upon this point are still needed before this can be stated dogmatically. Certainly so long as a positive value persists, even though a very low one, continued follow-up studies are essential.

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Chance favors the prepared mind.—*Pasteur.*

Diagnostic errors are more often due to laziness than to ignorance.

One thing the consultant can always do that has not been done—a rectal examination.—*Osler.*

WAR DERMATOLOGY: SOME GENERAL ASPECTS*

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THIS paper is part of a symposium prepared by the Committee on War Dermatology of the Los Angeles Dermatological Society, the purpose of which is two-fold: First, to acquaint the dermatologist with some of the problems which he is likely to encounter in the immediate future in either civilian or military practice; and second, to acquaint the medical profession with the part which dermatologists are ready and able to perform in this emergency.

The symposium included discussions on the treatment of burns, war gases, contact dermatitis, syphilis, and infections and infestations. This paper concerns itself with the diagnosis and treatment of some of the more common infections and infestations.

Cutaneous disorders due to infections and infestations, while frequently of a minor nature, are of considerable importance for the following reasons:

- (a) Large numbers of men are frequently affected by parasitic infestations, with a consequent lowering of efficiency and morale.
- (b) Many of the parasites are capable of transmitting contagious and epidemic diseases.
- (c) Secondary pyogenic infections are common, and may be serious and disabling.

1. Pediculosis corporis

Parasite—*Pediculus humanus corporis*.

Incidence—Extremely common under war conditions.

Symptoms—Itching, urticated papules, linear scratch marks, superficial pustules, deep abscesses, ecthyma, melanoderma, vitiligo. Eggs in underwear, clothing, but may be attached to body hairs.

Treatment

- (a) Hot soap and water bath, followed by suitable application to kill eggs which may be attached to body hairs, as Cuprex (Merck) which is allowed to remain on skin for 30 minutes and washed off, or
- (b) Rotenone lotion (2 per cent) which has been found effective in treatment of scabies, chigger bites, and other insect pests. Has not had extensive trial in pediculosis. (See under Chiggers.)

Prophylaxis

- (a) Disinfection of clothing by steam at 220° F. at 5 lbs. pressure for 30 minutes.
- (b) Possibly the occasional applications of 2 per cent rotenone lotion might discourage infestation.

* Read before the Section on Dermatology and Syphilology, at the Seventy-first Annual Session of the California Medical Association, Del Monte, May 3-6, 1942.